REMARKS

Claims 21-22 are pending in the application. No claim is allowed.

Claims 21-22 are rejected under 35 USC 103(a) as allegedly being unpatentable over Hanada et al. ("Hanada"), EP 0 493 737, newly cited, in view of Prisell et al. ("Prisell"), *Int. J. Pharma.*, **1992**, 85:51-56, of record. Applicant respectfully traverses the rejection and requests that it be reconsidered and withdrawn.

Hanada discloses a solution containing an analog of bFGF that is dripped onto bone after opening an incision to expose the bone. As the examiner observes, the compositions in Hanada do not contain hyaluronic acid. The examiner relies upon Prisell to show that a composition of IGF-1 growth factor in hyaluronic acid exhibits a slow release of the factor from the composition. The examiner concludes from these alleged teachings that the retarded release of bFGF from HA is sufficient to enhance, promote or increase bone growth when injected or applied to an injured, abnormal or diseased bone site.

Applicant respectfully disagrees with the examiner. Prisell's study is about diffusion of a peptide, IGF-1, from a composition of hyaluronan. There is no suggestion as to how the hyaluronan affects activity. In fact, Prisell does not even know if IGF-1 has any activity in the experiment. See page 55, left lines 30-32. Moreover, there is no discussion as to what happens to the hyaluronan after it is injected subcutaneously. That is because Prisell can only trace the migration of the IGF-1 which is radioactively tagged. The present invention deals with the persistence at the bone wound or defect site of the *composition* that includes both the HA and the bFGF, as a function of the composition's viscosity and biodegradability. In that light, the rate at which bFGF diffuses through HA teaches little, if anything relevant at all, to one of ordinary skill in the art about such persistence of the entire composition. In fact Hanada completely ignores the issue of persistence of the bFGF composition at the bone defect site. Hanada uses drops of a phosphate-buffered saline solution of bFGF to drip onto the site, then closes the wound and never applies the bFGF again during the experiments. Prisell measures the migration of a radioactively labeled peptide through an animal's leg from a subcutaneous injection of HA+the peptide. It is submitted that one of ordinary skill in the art would take from these teachings that dripping bFGF on a wound site is sufficient (Hanada) to accelerate bone growth. The teaching from Prisell is unclear. One would need to make several assumptions and speculate, but perhaps a subcutaneous injection of an active substance could

migrate toward a wound site. It is not seen how this would improve on Hanada's invention. Even Prisell can only speculate on what their experiment means. Page 55, ultimate paragraph.

For the foregoing reasons it is submitted that the claimed invention would not have been obvious under 35 USC 103(a) over the combination of Hanada and Prisell to one of ordinary skill in the art at the time the invention was made. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 21-22 are rejected under 35 USC 103(a) as allegedly being unpatentable over Nagai et al. ("Nagai"), *Bone* **1995**, 16:367-373, newly cited, in view of Prisell et al. ("Prisell"), *Int. J. Pharma.*, **1992**, 85:51-56, of record. Applicant respectfully traverses the rejection and requests that it be reconsidered and withdrawn.

Nagai discloses a solution containing recombinant bFGF that is intravenously injected daily for seven days into rats. Among other effects, increased longitudinal bone growth in the rats is observed. As the examiner observes, the compositions in Nagai do not contain hyaluronic acid. The examiner relies upon Prisell to show that a composition of IGF-1 growth factor in hyaluronic acid exhibits a slow release of the factor from the composition. The examiner concludes from these alleged teachings that the retarded release of bFGF from HA is sufficient to enhance, promote or increase bone growth when injected or applied to an injured, abnormal or diseased bone site.

Applicant respectfully disagrees with the examiner. Prisell's study is about diffusion of a peptide, IGF-1, from a composition of hyaluronan. The deficiencies of the teachings in Prisell have been discussed above and are incorporated herein in response to the rejection based on Nagai and Prisell. Nagai is not concerned with persistence at a bone defect site because there is no target site for their experiments. They are concerned with systemic effects on the whole animal. In a sense, both Nagai and Prisell miss the target. Nagai teaches that if one wants systemic bone growth, inject bFGF intravenously. Prisell speculates that a subcutaneous injection of a hyaluronan composition containing a factor slows the migration of the factor into the tissues. It seems that Nagai and Prisell are consistent with each other to that extent. But for that reason, one of ordinary skill would be led away from using Prisell's hyaluronan composition because systemic effects would probably be more effectively and efficiently attained by intravenous introduction rather than from a slow-migrating factor in a subcutaneous hyaluronan composition.

For the foregoing reasons it is submitted that the claimed invention would not have been obvious under 35 USC 103(a) over the combination of Nagai and Prisell to one of ordinary skill in

the art at the time the invention was made. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 21-22 are rejected under 35 USC 103(a) as allegedly being unpatentable over Nakamura et al. ("Nakamura"), *Encocrinol.* **1995**, 136:1276-1284, newly cited, in view of Prisell et al. ("Prisell"), *Int. J. Pharma.*, **1992**, 85:51-56, of record. Applicant respectfully traverses the rejection and requests that it be reconsidered and withdrawn.

Nakamura discloses a solution containing recombinant bFGF that is intravenously injected daily for seven days into rats. Among other effects, increased endosteal bone formation in the rats is observed. As the examiner observes, the compositions in Nakamura do not contain hyaluronic acid. The examiner relies upon Prisell to show that a composition of IGF-1 growth factor in hyaluronic acid exhibits a slow release of the factor from the composition. The examiner concludes from these alleged teachings that the retarded release of bFGF from HA is sufficient to enhance, promote or increase bone growth when injected or applied to an injured, abnormal or diseased bone site.

Applicant respectfully disagrees with the examiner. Prisell's study is about diffusion of a peptide, IGF-1, from a composition of hyaluronan. The deficiencies of the teachings in Prisell have been discussed above and are incorporated herein in response to the rejection based on Nakamura and Prisell. Like Nagai, Nakamura is not concerned with persistence at a bone defect site because there is no target site for their experiments. They are concerned with systemic effects on the whole animal. Nakamura teaches that if one wants systemic bone growth, inject bFGF intravenously. Prisell speculates that a subcutaneous injection of a hyaluronan composition containing a factor slows the migration of the factor into the tissues. It seems that Nakamura and Prisell are consistent with each other to that extent. But for that reason, one of ordinary skill would be led away from using Prisell's hyaluronan composition because systemic effects would probably be more effectively and efficiently attained by intravenous introduction rather than from a slow-migrating factor in a subcutaneous hyaluronan composition.

For the foregoing reasons it is submitted that the claimed invention would not have been obvious under 35 USC 103(a) over the combination of Nakamura and Prisell to one of ordinary skill in the art at the time the invention was made. Accordingly, withdrawal of the rejection is respectfully requested.

Applicant hereby petitions for any extension of time that may be required to maintain the pendency of this case, and any required fee for such extension or any further fee required in

connection with the filing of this amendment is to be charged to Deposit Account No. 504480 (Order No. DEPYP003D1C1).

Respectfully submitted,
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